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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,867	02/04/2002	Halle Morton	999710000008	3108

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EXAMINER	
SEHARASEYON, JEGATHEESAN	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,867	MORTON ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon, Ph.D	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11 and 25-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11 and 25-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/31/2006 has been entered. An action on the RCE follows.

2. Claims 1, 8-11, 25-28, 30-33 and 35 have been amended. Claims 37-42 have been added. Therefore claims 1, 3-11 and 25-42 are pending and under consideration.

3. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

4. The rejections not expressly recited are withdrawn.

Claim Rejections - 35 USC § 103, maintained

4. The rejection of claims 1, 3-11 and 25-36 under 103(a) as unpatentable over Morton et al. (WO 95/15338) in view of the M.S. study (Neurology, 1993) is maintained for reasons of record in the Office Actions dated 5 August 2003, 5 October 2004, 27 April 2005 and 1 February 2006 and is applied to new claims 37-42. Applicants have incorrectly indicated that claims 26-36 were not under this rejection (see page of the response). Applicants advised to review the Office Action of 1 February 2006 page 2, paragraph 4 for the applicable rejection.

The claims require treating multiple sclerosis by administering cpn10 and IFN-β, wherein the therapeutic effect of administering cpn10 and IFN-β together is

synergistically improved compared to therapeutic effect of administering the same equivalent amount cpn 10 or IFN-β alone. Applicants assert that neither the Morton reference nor the MS study, nor the combination thereof, teaches or suggests that combined cpn 10 and IFN-β treatment of MS or delay relapse following cessation of other treatments.

Applicants again assert that based on the expert declaration provided by Dr. Barbara Johnson, cpn10 and IFN-β act via different biological mechanisms to reduce MS symptoms and decrease relapse frequency. In addition, Applicants claim that Dr. Johnson's declaration asserts that the art implicitly taught away from the present invention by teaching that cpn10 and IFN-β have same biological mechanism of action (applicants have provided Jeffrey et al, 2004). Applicants' arguments have been fully considered but have not been found to be persuasive.

While Applicants are correct in asserting that the prior art does not disclose the administration of cpn10 and IFN-β together, as disclosed previously in the Office Actions dated 5 August 2003 (pages 4-5) and 1 February 2006 (pages 4-6), *In re Kerkhoven* (205 USPQ 1069, CCPA 1980) summarizes:

"It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form a combination that is to be used for the very same purpose: the idea of combining them flows logically from their having been individually taught in the prior art".

Although, Applicants recite that the therapeutic effect of administering cpn10 and IFN-β together is synergistically improved compared to therapeutic effect of

administering the same equivalent amount cpn 10 or IFN-β alone, the evidence presented in Figures 8, 9 and Table 4 does not support this assertion. Figures 8 and 9, which are the two figures that compare combinations to individual administration, do not indicate that there is any unexpected benefit from this combination. Figure 8 shows an uneven progression with substantial overlap in the methods of treatment. Figure 9 shows a very modest difference. In addition, the mean disability score for the primary attack is reported on Table 4 to be 14.1 ± 2.3 (cpn10 alone), 17.4 ± 2.5 (IFN-β alone) and 13.6 ± 2.1 (cpn10 and IFN-β together). Similarly, the mean disability score for the "period of relapse" is reported on Table 4 to be 24.6 ± 8.2 (cpn10 alone), 27.1 ± 8.5 (IFN-β alone) and 17.9 ± 10.9 (cpn10 and IFN-β together). The artisan would expect at least an additive effect but the data shows very little advantage to the combination. Specifically, the co administration data appears to be statistically not significant compared to cpn-10 or IFN-β alone. There is no evidence of a synergistic effect. Thus there is no teaching of a result that would be unexpected from the combination of two agents that are useful for the same purpose, which combination itself is *prima facie* obvious for the reasons set forth in the previous office action(s).

Contrary to Dr. Johnson's declaration that the invention achieves the beneficial and synergistic result by using doses of each agent lower than would have been regarded as the optimal dose for each agent used alone (Paragraph 13 of the declaration), there is no evidence of synergy. It is argued that 2.5 μg of cpm10 administration in one aspect of the methods of the invention can be considered a suboptimal dose (because the Morton reference discloses the administration of 15μg of

cpm10 to a mouse on page 21, line 23). However, the 2.5 μg of cpn-10 administered to a 40g mouse (average adult mouse weight) in Example 6, is actually about 62.5 μg/kg body weight, which has been previously disclosed on page 27, lines 14-15 of Morton et al. (WO 95/15338). The administration of 5000 IU to a 40g mouse is equivalent to 8.75 MIU (a 70 kg adult), which is taught by the M.S. study refrence. Applicants also argue that neither Morton nor the MS study teach or suggest administering IFN-β in combination therapy to allow the IFN-β to be administered at dosages which would be clinically ineffective if IFN-β were to given alone. However, this argument is not found to be persuasive because it is routine in the art to optimize the dosage administered to a patient to obtain optimal clinical outcome and thus it is not inventive.

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.").

With respect to Applicants claim that Dr. Johnson's declaration notes that the art (Jeffery et al., 2004) taught away from the present invention by "the agent added to the primary therapy may have no effect, or, worse, may antagonize the effect of the primary agent". It also goes on to say that in many instances whilst one may assume that the combination of two agents may have a beneficial effect, the opposite may be true.

However, the complete reading of the article does not teach away from combination therapy and suggests that studies are needed to address the question of whether there is an additive or synergistic effect and to address the long-term safety of the combination. In any event there is no teaching in Jeffrey et al. to cast doubt in combining cpn 10 and IFN-β.

Applicants further assert that they have submitted sufficient evidence, including Dr. Johnson's declaration, to indicate that there was a long-felt need for an invention such as that claimed in this application. However, declaration under 37 CFR 1.132 is insufficient to overcome the obviousness rejection, because there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. Specifically data shows very little advantage to the combination therapy to that of administering cpm or IFN-β alone as argued above. The Applicants are encouraged to refer to MPEP § 716.04 to address issues relating to long-felt need in the art.

Claim Rejections - 35 USC § 112, second paragraph maintained.

5. The rejection of claim 31 as vague and indefinite for reciting the phrase "clinically significant IFN-β-induced side effects in the individual " is maintained for reasons set forth in the Office Action dated 1 February 2006 (see 8c). The original rejection had claims 25, 31 and 32. However, Applicants amended claims 25 and 32 to obviate the rejection. Applicants have argued, "what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail in the specification". However, it is unclear what is a clinically significant IFN-β-induced side effect in the

individual is? Specifically it is unclear of the many side effects associated with IFN-β, which are clinically significant. Therefore, the rejections of record are maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112, second paragraph (New).

6.Claims 33-36 are rejected as vague and indefinite for reciting the term "equivalent of administering" is not defined in the specification. The artisan would be unable to determine what amounts Applicants intended the claims to encompass. Is the pharmaceutically effective amount different from the equivalent amount?

Claim Rejections - 35 USC § 112, first paragraph

7. Claim 1, 3-11, 27-31 and 33-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of MS by administration of cpn 10 and IFN-β, does not reasonably provide enablement for the synergistically improved treatment of MS. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte Forman,* (230 USPQ 546 (Bd Pat. App. & Int. 1986)); *In re Wands,* 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The claim 1 requires the treating of multiple sclerosis by administering cpn10 and IFN-β, wherein the therapeutic effect of administering cpn10 and IFN-β together is synergistically improved compared to therapeutic effect of administering the same equivalent amount cpn 10 or IFN-β alone. Both the specification and the prior art teach that IFN-β and cpn 10 can be used to treat M.S by administering either IFN-β and cpn 10. Although, Applicants recite that the therapeutic effect of administering cpn10 and IFN-β together is synergistically improved compared to therapeutic effect of administering the same equivalent amount cpn 10 or IFN-β alone, the evidence presented in Figures 8, 9 and Table 4 does not support this assertion. Figures 8 and 9, which are the two figures that compare combinations to individual administration, do not indicate that there is any unexpected benefit from this combination. Figure 8 shows an uneven progression with substantial overlap in the methods of treatment. Figure 9 shows a very modest difference. In addition, the mean disability score for the primary attack is reported on Table 4 to be 14.1 ± 2.3 (cpn10 alone), 17.4 ± 2.5 (IFN-β alone) and 13.6 ± 2.1 (cpn10 and IFN-β together). Similarly, the mean disability score for the "period of relapse" is reported on Table 4 to be 24.6 ± 8.2 (cpn10 alone), 27.1 ± 8.5 (IFN-β alone) and 17.9 ± 10.9 (cpn10 and IFN-β together). The artisan would expect at least an additive effect but the data shows very little advantage to the combination. Specifically, the co administration data appears to be statistically not significant compared to cpm or IFN-β alone. There is no evidence of a synergistic effect. See enclosed discussion on synergism (Katzung et al.1992, page 706). There is no guidance in the specification to indicate how one would obtain the synergistic effect.

Thus, an undue amount of experimentation would be required for the co administration of cpn 10 and IFN-β to generate synergistic effect.

Given the breadth of claim 1 in light of the unpredictability of the art as determined by the lack of working examples, the level of skill of the artisan, and the lack of guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention of co administration of cpn 10 and IFN-β for the synergistic therapeutic effect of MS.

8. No claims are allowable.

Contact information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon, Ph.D whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JS 06/06

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